Original Article

Convalescent plasma therapy in COVID-19 and discharge status: A systematic review

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Abstract

Objective: Covid19 has emerged as a greatest threat of the decade worldwide. At present there is no certain treatment for treating coronavirus diseases, while some antiviral drugs (Remdesivir , Lopinavir and Ritonavir) are under investigation. Many countries including India have adopted the convalescent plasma therapy in the treatment of moderate to severely ill patients. Despite the treatment being given ,there are no such evidences on the utility and efficacy of convalescent plasma.Hence this study tries to find out the impact on the discharge status from hospital of the patients receiving the very therapy. **Design:** Systematic review and meta analysis. **Setting:** An extensive search was made, following PRISMA guidelines on online databases such as Pubmed, Google scholar and Science direct.Studies those fulfilled the inclusion and exclusion criteria ,were included and reviewed and analyzed for a common outcome(discharge status). **Participants:** A total of 6 eligible studies were analyzed qualitatively and quantitatively which included three case control, two case series and one case report. **Results:** The overall pooled discharge rate from the above studies was 75.7% after the CP therapy. When analyzed for relative risk , it showed CP therapy having a lower risk of staying in hospital (not getting discharged) when compared to Standard therapy ,overall RR (relative risk) being 0.946. **Conclusion:** Our study shows that there is always a higher rate of discharge and low risk of prolonged hospital stay in those patients who receive plasma therapy. CP therapy being a low cost and easy to administer therapy with very less adverse events, requires more focus on further research as it has a potential to become an ideal effective treatment option for COVID-19.

Keywords: Convalescent plasma, COVID-19, discharge status, plasma therapy

Background

By late 2019, the outbreak of coronavirus disease-2019 (COVID-19) was unchecked in China.[1] and now it affected 213 countries and territories around the world.[2] On March 11, 2020, it was declared a pandemic by the World Health Organization (WHO). Till the time of writing of the manuscript, the total number of cases in the world was nearly 68,651,512 with a recovery rate of 97.73% and death rate around 2.27%. By this time, India ranked on the second position with total number of cases 9,735,975 and total number of death 141,398 (1.45%).[2] As stated by WHO that globally the death rate was 3.4% in reported COVID-19 cases in March which has become 3.74% on sixth August and has come down to around 2.2% in December.[2,3] It was observed that the mortality is more in aged (>65) and with underlying medical condition (include diabetes, lung disease, cancer, immunodeficiency, heart disease, hypertension, asthma, kidney disease, GI/liver disease, and obesity).[4] Many patients with COVID-19 develop severe acute respiratory illness with urgent need of mechanical ventilation and admission in ICU (intensive care unit) because mortality in these patients varies from 10% to 40% which is much higher than the overall percentage.[5-7] At present, there is no certain treatment for treating coronavirus diseases, whereas some antiviral drugs (remdesivir, lopinavir, and ritonavir) are under investigation.[8]

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COVID-19 shows similarities and differences with severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). They all are responsible for lower respiratory infection and can cause acute respiratory distress syndromes (ARDS).[9] It is seen that convalescent plasma (CP) from the patients has been used for the prevention and treatment of many infectious diseases. Findings from a meta-analysis from 32 studies suggested that after CP, therapy there was a statistically significant reduction in mortality compared to placebo or no therapy.[10,11] Because coronavirus shows virological and clinical similarities with SARS and MERS and evidence shows that CP from patients who have recovered from viral infections can be used as a treatment without the occurrence of severe adverse events. Therefore, it might be worthwhile to test the safety and efficacy of CP transfusion in SARS-CoV-2-infected patients.[12] No systematic review exclusively on "Convalescent plasma therapy for COVID-19" has been done in India till date as per our knowledge. Also, we were not able to find any such exclusive systematic review published worldwide. Although the number of cases has declined but still one can find a case anywhere in any setting, also the presenting symptoms are quite variable indicating a focused attention of any physician, even those who are giving primary care. The knowledge regarding effective treatment can change the outcome if the right decision is taken at the right time. Hence, the study was considered, assuming that it would provide an unprecedented step in the treatment of the very much feared disease.

Methods

This systematic review and meta-analysis follows PRISMA (preferred reporting items for systematic reviews and meta-analysis).[13]

Study selection

We included the studies of patients having an infection of COVID-19 and received plasma therapy for their treatment. Eligible studies had minimum of 1 dose of CP/hyperimmune immunoglobulin along with standard therapy with or without comparators. All the studies that were included were recent (2020) only.

Outcome of interest included reverse transcriptase polymerase chain reaction (RT-PCR) result, discharge from hospital and length of hospital stay/Not getting discharged. We did not include adverse effects of the therapy such as complications related to intravascular volume overload, allergy or other serious events. For each patient population, we included all the studies irrespective of design. The studies that were found during the search were mostly case series/case report and case controls. As we were unable to find RCTs about

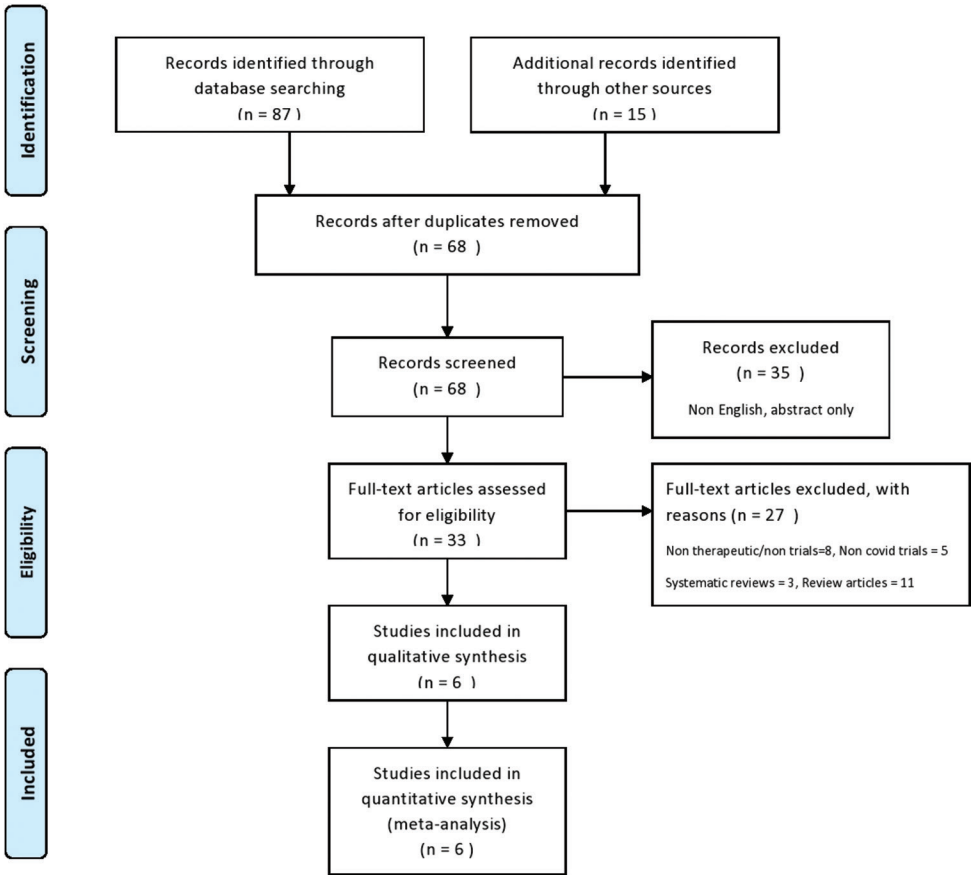

Figure 1: PRISMA flow chart for study selection

plasma therapy in COVID-19 we included all those that were satisfying the criteria.

Data sources, searches, and extraction

Two reviewers searched for relevant articles from data sources such as PubMed, PubMed Central, Google Scholar, and ScienceDirect. The search was started on April 27, 2020 and two full months were dedicated (till June 30, 2020) for data search and extraction. The advanced search feature of PubMed was used with MeSH terms and Boolean logic to search for the manuscripts in PubMed. Similarly, searches were made by both the reviewers on Google Scholar and ScienceDirect. The keywords used were COVID-19, coronavirus, SARS Co-2, novel coronavirus, plasma transfusion, plasma therapy, passive transfusion, immunotherapy, CP, passive antibody. The initial search results showed 3,54,098 studies on PubMed, 9530 on Google Scholar and 76 on ScienceDirect, based on relevance and other characteristics. Of the above-searched results potentially eligible studies were 87. After removing duplicates, and other studies [refer Figure 1], full texts included in qualitative and quantitative synthesis were 6.

However, some recent trials have shown inconsistent findings like a study done on 103 patients by Ling Li *et al.*[14] showed that Among patients with severe or life-threatening COVID-19, CP therapy added to standard treatment, compared with standard treatment alone, did not result in a significant improvement in time to clinical improvement within 28 days. Contrasting to the above example, a pilot study done by Kai Duan *et al.*[11] suggested that One dose of CP with a high concentration of neutralizing antibodies can rapidly reduce the viral load and tends to improve clinical outcomes.

Results

Dose of convalescent plasma

The dose of CP varied from 200 mL per dose (transfusion) to 300 mL per dose (transfusion). Number of doses also varied

Table 1: Characteristics of the included studies

Study, year, country	Study design	Convalescent plasma	Sample size	Median age	Outcome	Time taken to recover after CP (Mean)	Status
Duan *et al.*, 2020, China[11]	Case Control	200 mL of inactivated CP	10 case 10 controls	53.4 years	RT-PCR negative	2 days	*3 discharge (30%)
Shen *et al.*, 2020, China[15]	Case series	2 consecutive transfusions of 200 to 250 mL (400 mL of convalescent plasma in total)	5	50 s (not specified, hence mean age of 50 years was taken as a mean)	RT-PCR negative	6.2 days	3 discharge 2 Hospitalized (60%)
Zhang *et al.*, 2020, China[16]	Case series	300 mL × 3 doses 200 mL × 1 dose 300 mL × 8 dose 300 mL × 1 dose	4	57 years	RT-PCR negative	20.5 days	Discharge Discharge Hospitalized Discharge
Ahn *et al.*, 2020, Korea[17]	Case report	250 mL × 2 doses	2	69 years	RT-PCR negative	12 days	Discharge *Hospitalized
Ye *et al.*, 2020, China[18]	Case series	200 mL × 3 doses 200 mL × 2 doses 200 mL × 3 doses 200 mL × 1 dose 200 mL × 1 dose 200 mL × 1 dose	6	63 years	RT-PCR negative	8.16 days	Discharge Discharge Hospitalized Discharge Discharge Discharge
Liu *et al.*, United States of America[19]	Case Control	250 mL × 2 doses	39 cases 156 controls (1:4), 76 controls (1:2)	55 years	RT-PCR negative	11 days	28 discharge 6 Hospitalized 5 deaths

mL=milliliter, RT-PCR=reverse transcriptase polymerase chain reaction. *weaned off from mechanical ventilation, *three discharged and seven were about to discharged

Table 2: A Comparison of RR (relative risk) of not getting discharged from case control studies

Study	Year	RR (95% CI)	OR (95% CI)	Events, convalescent plasma	Events, standard care
Duan *et al.*	2020	0.778 (0.493-1.226)	0.259 (0.02-3.06)	7/10	9/10
Liu *et al.*	2020	0.846 (0.489-1.463)	0.785 (0.3628-1.7017)	11/39	52/156
Liu *et al.*	2020	0.916 (0.502-1.672)	0.883 (0.378-2.062)	11/39	24/78
Subtotal		0.946 (0.670-1.334)	0.919 (0.548-1.541)	29/88	85/244

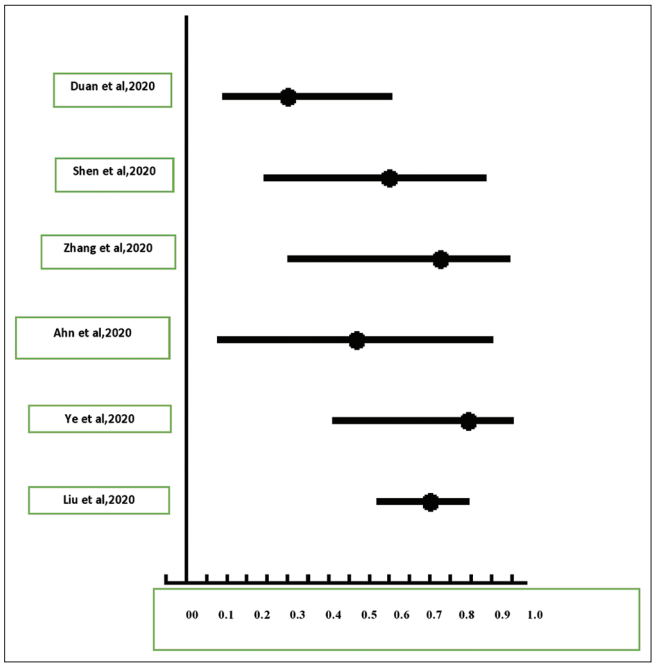

Figure 2: A comparison of discharge proportion from all of the included studies

from center to center. Minimum no. of transfusions were 1 to a maximum of 8 (varied from study to study [Table 1]).

Mean age of the participants

The mean age from all the studies came out to be 57.93 years. It was highest in the study by Ahn *et al.*[17] (69 years) and lowest in the study by Shen *et al.*[15] (50 years) although it was not specified in the study [Table 1].

Time taken to recover after CP (Mean)

The average time taken to recover after CP administration was 9.97 days. It was lowest (2 days) in the study by Duan *et al.*,[11] and was highest (11 days) in the study by Liu *et al.*[19]

Outcome status

The overall pooled discharge rate from the above studies was 75.7% after the CP administration. In Duan *et al.'s*[11] study, the discharge rate was 30%, 83% in Ye *et al.'s*[18] study, 75% in Zhang *et al.'s*[16] study and only 50% in the case report by Ahn *et al.*[17] [Figure 2]. As evident in Table 2, when only case control studies were considered, we got 3 studies (Duan *et al.*[11]) and two from Liu *et al.*[18] (1:4 and 1:2). When analyzed for relative risk, it showed CP therapy having a lower risk of staying in hospital (not getting discharged) when compared to standard therapy, overall RR (relative risk) being 0.946. [Figure 3]

Data quality assessment

Risk of bias assessment for case series

Of the included six studies, four were case series. For the quality assessment of those studies, a 13-item assessment scale was used which included sample type, inclusion/exclusion criteria,

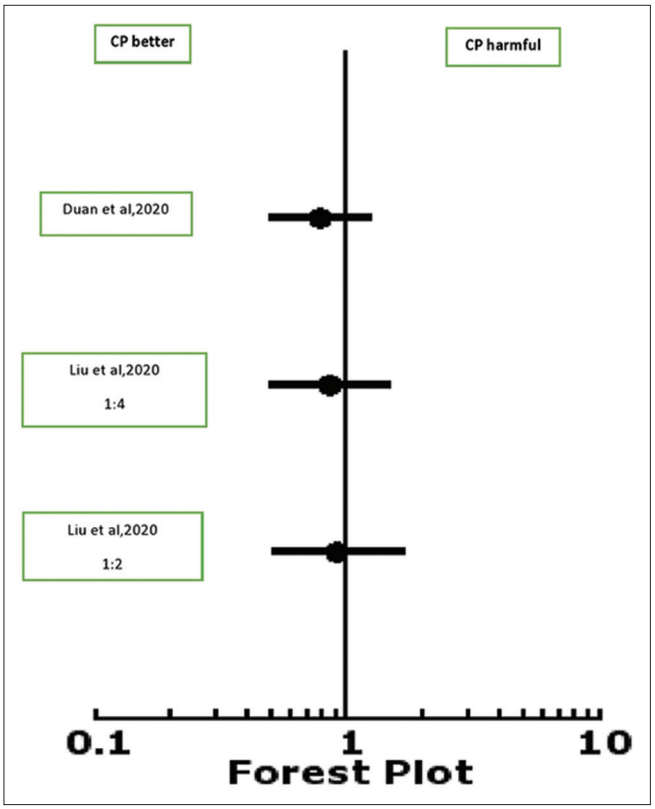

Figure 3: Forest plot showing relative risk (RR) of getting not discharged from hospital

similar participants, consecutive selection, prospective data collection, intervention, study setting, outcomes, follow-up, nonrespondents, and prognostic factors.[20] A study satisfying more than 10 criteria (>75%) was considered as a study with low risk of bias while a study satisfying less than 8 (60%) was considered as a study with high risk of bias.

Risk of bias assessment for comparative studies

Of the included six studies, three (Liu *et al.*[9] had two control types) were comparative (case control) studies. For the quality assessment of those studies, an 18 item assessment scale was used which included sample type, Inclusion/exclusion criteria, similar participants, consecutive selection, prospective data collection, intervention, study setting, outcomes, follow-up, nonrespondents, comparability of groups, and prognostic factors.[20] A study satisfying more than 14 criteria (>75%) was considered as a study with low risk of bias while a study satisfying less than 11 (60%) was considered as a study with high risk of bias.

Interpretation

The included studies provided only low-quality evidence to support the inferences regarding the efficacy of CP in the management of COVID-19. On March 25, 2020, the US food and drug administration approved the use of CP for COVID-19 under the emergency investigational new drug category and not for routine clinical use. The inclusion of the findings cannot be used as a demonstrated efficacy because of the lack of clinical

trials (RCTs) or Case control studies. The three case-control studies provided a relative risk of not getting discharged/prolonged hospital stay which was lower in the CP recipients.

Strengths of this systematic review was a comprehensive search made by the separate researchers across most of the databases for the relevant studies and all the included studies were exclusive for COVID-19 treatment using CP with other supporting therapies (antivirals, steroids, antibiotics, and O2) and recent from the year 2020 only. Although we could not limit the risk of bias by excluding single-arm studies as we had only six studies fulfilling our criteria and four of six studies were single-armed (case series and case reports).

Conclusion

The main advantage of CP transfusion is it is very low rate of adverse events, Also this has some added advantages over the unproven therapies for COVID-19. Due to the unavailability of sufficient evidences, the comment on efficacy could not be done. Hence for testing the efficacy, trials should be prioritized as this therapy has the potential to be developed into a safe and effective treatment modality. A multicentric trial of CP administration in the treatment of COVID-19 has already begun including our parent institution (AIIMS, Patna). Our systematic review of the available literature shows that there is always a higher rate of discharge and low risk of prolonged hospital stay in those patients who receive plasma therapy. In other words, it can be said that hospital discharge time decreases in the patients who receive plasma therapy along with the standard therapy for COVID-19.

Limitation

As there were very few studies available till the time the manuscript was being written, only six studies were included in the review. Also the design of the studies was not common. Another limitation was the absence of control/comparator in most off the studies because of which comment on the efficacy could not be done. The third limitation was the quality of evidences from the individual studies as some of those were weak (having only two, four, or five cases).

Registration

Prospero registration done, Registration ID-CRD42020203496.

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Conflicts of interest

There are no conflicts of interest.

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